Develop New or Improved Methods for Diagnosing Disease and Disability

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Rapid Method for Diagnosing Familial Transthyretin Amyloidosis

Background: Transthyretin is an important transport protein in the blood. Genetic variations in this protein can cause an inherited condition called "familial transthyretin amyloidosis," or ATTR. In this disease, variant or normal versions of transthyretin or their fragments stick together, forming amyloid fibrils that are deposited in the heart, along peripheral nerves, and in the eye, among other sites. Death occurs within 7 to 15 years after the appearance of symptoms. The most effective treatment for the disease is liver transplantation. Diagnosis requires determining the complete amino acid sequence of a patient's transthyretin in order to identify the specific defects in the protein.

Advance: Scientists at the NIH-supported Mass Spectrometry Resource for Biology and Medicine at Boston University have developed a rapid method for diagnosing ATTR by analyzing patients' transthyretin. Ordinarily, a protein sequence is analyzed by first using an enzyme to cut the protein into peptides containing only a few amino acids and then determining the amino acid sequence of each peptide. However, this process is time-consuming, and protein sections are often missed. To quickly analyze the entire amino acid sequence of transthyretin, the Boston University lab uses multiple enzymes to digest transthyretin and multiple types of mass spectrometry. This method allows for rapid analysis of the entire transthyretin sequence and provides the information necessary for a diagnosis.

Implications: Sophisticated mass spectrometric methods are the only way to determine complete transthyretin sequences, which are critical for correctly diagnosing ATTR. Besides this work on diagnostic techniques, the Boston University researchers are also compiling a library of transthyretin genetic variants, which is leading to an improved understanding of the disease process.

Lim A, Prokaeva T, McComb ME, O'Connor PB, Theberge R, Connors LH, Skinner M, Costello CE: Characterization of transthyretin variants in familial transthyretin amyloidosis by mass spectrometric peptide mapping and DNA sequence analysis. Analytical Chemistry 74: 741-751, 2002.

Injected Insulin Fails to Prevent Type 1 Diabetes in High Risk Patients

Background: The immune systems of patients with type 1 diabetes have inappropriately attacked and destroyed the insulin-producing beta cells, found clustered within pancreatic structures known as islets. Without beta cells, patients lose the ability to secrete insulin in response to food intake. Relatives of type 1 diabetes patients are at an increased risk of developing the disease, because their genes may predispose the immune system to attack and destroy the pancreatic islets. A test that identifies persons with high levels of anti-islet antibodies, combined with assessment of insulin secreting capacity through metabolic testing, can predict risk for the development of type 1 diabetes. Based on animal data and very small pilot studies in human, many patients and providers hoped and believed that administering very low dose injections of insulin to those at highest risk of developing the disease might prevent onset of diabetes, either by allowing the struggling beta cells to rest or by altering the immune system by an as yet unknown mechanism. In fact, some doctors began treating high risk patients with insulin, even though its usefulness in preventing type 1 diabetes had not been adequately tested.

Advance: In a randomized, controlled clinical trial, researchers tested the hypothesis that injected insulin can prevent type 1 diabetes in those most at risk. Relatives of type 1 diabetes patients with anti-islet antibodies and other genetic, metabolic, and immunologic indicators of susceptibility to the disease were assigned to either an insulin-injection or an observational group. Those in the former group received low dose injections of slow-acting insulin twice every day, in addition to yearly, four-day continuous intravenous insulin infusions. Participants were tested every six months to determine whether or not their bodies were able to effectively manage blood sugar. The insulin treatment did not cause dangerously low blood sugar (hypoglycemia) that could arise if insulin levels were too high. After an average follow-up of 3.7 years, the results demonstrated no significant difference in the number who developed type 1 diabetes in the insulin-injection group *versus* the observational group. In designing this study, the researchers believed that they could accurately identify a very high-risk group of relatives, half of whom would develop type 1 diabetes over the course of five years. In fact, based on information derived form years of careful previous studies, the trial showed that they could accurately identify such a high-risk group.

Implications: This trial unequivocally disproved the hypothesis that injected insulin can prevent type 1 diabetes in those at risk, thus potentially sparing many patients from burdensome and ineffective therapy. It also clearly demonstrated that researchers can predict, with great reliability, which relatives of type 1 diabetes patients are most likely to develop the disease. This ability is important because it will allow researchers to design studies to test promising new preventive agents as they are developed or identified.

Diabetes Prevention Trial-Type 1 Diabetes Study Group: Effects of insulin in relatives of patients with type 1 diabetes mellitus. N Engl J Med 346(22): 1685-1691, 2002.

Safe, Inexpensive, Commonly Used Medical Technology Found to be Effective in Predicting Relapse to Alcohol and Drug Abuse

Background: Relapse to drug use, even after treatment has been successfully completed, is one of the hallmarks of drug addiction. It is costly to both society and the individual. Predicting whether an individual will relapse has been difficult to accomplish with any precision. Some studies suggest that severity of dependence as well as psychiatric co-morbidities are the best predictors of relapse, but other studies fail to confirm these findings. Inaccuracies in patients' memories or reports of prior drug use, and imprecision in psychiatric diagnoses may contribute to the disparities in such research. Therefore, the development of an objective measure to accurately predict an individual's likelihood of relapse could lead to more efficient and cost-effective approaches to relapse prevention.

Advance: 107 substance-dependent patients living in a residential treatment community, who had been abstinent from all substances, including alcohol, for at least 1 month and no more than 5 months, participated in this study. Five minute recordings of the resting brain activity were obtained by electroencephalography (EEG). This is measured by placing electrodes over the surface of the head, which can measure activity in the brain just below the skull. The EEG recordings were analyzed by region of the brain and frequency or rate of activity. The participants were evaluated over a period of 6 months by interviews and random breath and urine analyses. A number of variables were measured for their predictive value with respect to relapse, including demographic factors, psychiatric co-morbidities, family history, and severity of drug dependence. High frequency EEG activity (19.5-39.8 Hz; fast beta power) predicted relapse to drug use better than *all* other factors measured, and this result was true irrespective of the drug(s) of abuse.

Implications: These results suggest that a non-invasive and relatively inexpensive method of measuring brain function can accurately predict who is likely to relapse to substance abuse following treatment. Additional studies support and extend these findings for different substances of abuse, differing time points following drug or alcohol cessation, and alternative outcome measures (e.g., treatment retention, which may be a proxy marker of outcome). Quantitative EEG measurement could potentially become a valuable clinical tool for the efficient targeting of resources towards individuals identified as most in need of long-term treatment

Bauer L: Predicting relapse to alcohol and drug abuse via quantitative electroencephalography. Neuropsychopharmacology 25(3): 332-340, 2001.

Prichep LS: Outcome related electrophysiological subtypes of cocaine dependence. Clinical Electroencephalography 33: 8-20, 2002.

Transcriptomics: Patterns of Serotonin 2C Receptor Editing as a Marker of Suicide?

Background: The 5-HT2C serotonin receptor is widely distributed in the brain and is implicated in the regulation of mood and affective behavior. This receptor is unique not only among serotonin receptors but among the larger superfamily of G-protein coupled receptors, in that the pre-mRNA, which encodes the 5-HT2C receptor protein, can be edited by enzymes that alter the genetic sequence at five different sites (referred to as A, B, C', C, and D). Editing of the pre-mRNA at any combination of these five sites produces a receptor protein with altered signaling properties. The edited 5-HT2C receptors, referred to as isoforms, typically have a decreased ability to couple to second messenger signaling molecules in the cell resulting in a decrease in receptor function. There is emerging evidence that RNA transcripts are altered in psychiatric disorders and that these changes may contribute to the underlying pathophysiology.

Advance: In the present study, the investigators report that the pattern of 5-HT2C receptor editing is altered in the prefrontal cortex of people who have committed suicide. In the normal human brain, the most common pattern of editing occurs at the A site. In contrast, the pattern in suicide victims was increased editing at the C' and C sites, decreased editing at the D site, and very low levels of non-edited 5-HT2C mRNA in comparison with controls. These findings suggest an overall decrease in 5-HT2C receptor activity in the prefrontal cortex of suicide victims with a history of major depression. In parallel studies conducted in mice treated chronically with fluoxetine, the patterns of 5-HT2C receptor editing were opposite those seen in suicide victims, i.e., less editing at the C' and D sites and increased concentrations of the A edited isoforms. These results suggest that a serotonin-mediated mechanism may regulate editing of 5-HT2C receptor pre-mRNA.

Implications: The data suggest a role for 5-HT2C receptor pre-mRNA editing in the pathophysiology of suicide. Future studies will determine if differences in 5-HT2C receptor editing observed in human post-mortem brain from depressed suicide victims are independent of age of onset, number of depressive episodes, and previous drug treatment. Overall, these studies demonstrate the potential of genetic technology to dissect the biological processes leading to the pathophysiology of psychiatric disorders.

Gurevich I, Tamir H, Arango V, Dwork AJ, Mann JJ, and Schmauss C: Altered editing of serotonin 2C receptor pre-mRNA in the prefrontal cortex of depressed suicide victims. Neuron 34: 349-356, 2002.

Garlow SJ: And now, transcriptomics. Neuron 34: 327-328, 2002.

Triage for Women with Positive Pap Smear Results

Background: Every year, more than two million women in the United States receive a positive Pap smear result, but only about five to ten percent of these women actually have a cervical cancer precursor condition. Referring all women with positive test results for colposcopy (a more accurate diagnostic procedure) might be the safest course, but this would be costly, impractical, and anxiety producing. Therefore, alternative approaches to managing this population of patients have been sought.

It is known that persistent infection with certain strains of the humanpapilloma virus (HPV) are responsible for most cases of cervical cancer. Previous research also has shown that HPV infection decreases with age.

Advance: To help determine when to refer women for colposcopy if their Pap smears are positive for atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSILs), NIH researchers also tested for the presence of cancer-associated strains of HPV. A clinician conducted a pelvic examination and collected a cervical sample with which to prepare a thin-layer slide for HPV DNA testing. Gynecologists biopsied all lesions found via colposcopy to be suspicious for cancer or a precursor condition. The investigators found that HPV testing was highly sensitive for detecting cervical cancer and its precursors in women with ASCUS, but not in women with LSILs. The findings also showed that women with ASCUS aged 29 and older were far less likely to be HPV positive.

Implications: This study suggests that HPV testing would dramatically decrease colposcopy referrals in older women with ASCUS, but not LSILs. These findings could serve as the basis for triage and management recommendations for women whose Pap smear results are positive for ASCUS.

Sherman JE, Schiffman M, Cox JT: Effect of age and human papilloma viral load on colposcopy triage: data from the randomized atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion triage study (ALTS). Journal of the National Cancer Institute 94(2): 102-107, 2002.

New Molecular Test Appears Useful for Prognosis of Colorectal Cancer

Background: Health professionals rely mostly on histopathological staging (i.e. examining microscopic slices of tumor tissue in the laboratory) to estimate the chances that colorectal cancer might recur after surgery. Many scientists are looking to molecular markers, such as abnormalities in DNA, to develop a better prognostic tool. Previously, investigators from NIH's Special Program of Research Excellence (SPORE) discovered that patients with tumors that are missing certain pieces of chromosome 18q (known as "allelic imbalance") tend to progress more poorly. Until recently, however, it has been very difficult to accurately measure allelic imbalance in tumor tissue.

Advance: NIH SPORE investigators developed a highly sensitive and accurate assay, known as "digital SNP analysis," to measure allelic imbalance of two chromosomes, 18q and 8q. They used this test to show that allelic imbalance in these chromosomes was associated with recurrence of this disease. After 5 years of follow-up, 58 percent of patients with allelic imbalance in both chromosomes remained disease free, along with 74 percent of those with only one chromosome affected. All patients without allelic imbalance were disease free after 5 years, although routine histopathological staging would have predicted recurrence in at least some of these patients.

Implications: This new, highly sensitive test appears to provide a better prognostic indicator of colorectal cancer recurrence than the current standard of histopathological staging. Further research must show whether this type of technique will work as well for other cancer sites.

Zhou W, Goodman SN, Galizia G, Lieto E, Ferraraccio F, Pignatelli C, Purdie CA, Piris J, Morris R, Harrison DJ, Paty PB, Culliford A, Romans KE, Montgomery EA, Choti MA, Kinzler KW, Vogelstein B: Counting alleles to predict recurrence of early-stage colorectal cancers. Lancet 359: 219-225, 2002.

Zhou W, GaliziaG, Goodman SN, Romans KE, Kinzler KW, Vogelstein B, Choti MA, Montgomery EA: Counting alleles reveals a connection between chromosome 18q loss and vascular invasion. Nat Biotech 19(1): 78-81, 2001.

Early Detection of Osteoarthritis

Background: Osteoarthritis (OA), the most common degenerative joint disease, affects more than half of the population above the age of 65 and has a significant negative impact on the quality of life. The economic costs in the U.S. from OA include significant worker disability costs each year. The main cause of osteoarthritis is the degeneration of cartilage, the tissue that covers the bony ends in joints and withstands and distributes loads on the joints. Cartilage undergoes significant changes during the course of OA including softening, breakdown of materials that make up the cartilage, and eventual loss of cartilage all together. Although there is at present no cure for osteoarthritis, the debilitating effects of the disease can be minimized if it is diagnosed in its early stages. Currently, diagnosis of OA is made based on changes in x-ray (joint space width) or through histopathological examination of tissue sampled during invasive surgical procedures. A more accurate and preferably non-invasive method of examination is highly desirable.

Advance: Magnetic resonance imaging (MRI) is a technique whereby body tissues can be visualized through external exposure to strong and rotating magnetic fields. An image can be produced which can be studied at both a whole organ and structural (very detailed or microscopic) level. MRI measurements are sensitive to both the sodium ions and water present in cartilage. For the past several years, NIH-funded investigators have been developing techniques for the non-invasive detection and characterization of osteoarthritis using MRI. These MRI methods have been used to determine loss of cartilage under conditions that replicate the conditions of osteoarthritis and increase in cartilage matrix following treatment with glucosamine, a popular substance reported to build cartilage matrix. The changes observed under these varying conditions are then correlated with well-defined histopathological features of the cartilage. Such correlations will eventually result in a non-invasive system of MR classification to determine the changes in cartilage during all stages of osteoarthritis. The results of examining these tissue specimens to date have demonstrated that these methods are indeed capable of detecting the early degeneration of cartilage.

Implications: Although the widespread application of these techniques is not immediately possible, such findings show promise for future development of a routine diagnostic tool to be used in clinical studies for diagnosis of early osteoarthritis. These methods also provide non-invasive means for assessment of the efficacy of cartilage grafting, potential new therapies based on chondroprotective/disease modifying drugs, and food-like substances that have a medicinal effect for osteoarthritis.

Shapiro EM, Borthakur JH, Kaufman JS, Leigh JS, Reddy R.: Water Distribution Patterns Inside Bovine Articular Cartilage as Visualized by ^{1}H Magnetic Resonance Imaging. Osteoarthritis & Cartilage 9: 533-538, 2001.

Shapiro EM, Borthakur A., Gougoutas A., Reddy R.: ^{23}Na MRI Accurately Measures Fixed Charge Density in Articular Cartilage. Magn Reson Med 47: 284-291, 2002.

Akella SVS, Regatte RR, Gougoutas AJ, Borthakur A, Sharpiro EM, Kneeland JB, Leigh JS, Reddy R: Proteoglycan Induced Changes in $T_{1\rho}$-relaxation of Articular Cartilage at 4T. Magn Reson Med 46: 419-423, 2001.

Non-invasive Imaging Technique Used to Detect Recent Stroke

Background: Magnetic resonance imaging (MRI) is a noninvasive method that can be used to examine atherosclerotic lesions on the walls of the carotid arteries, the large arteries that provide blood to the brain. The lesions, or plaques, typically contain a large fat-filled core surrounded by a fibrous cap, similar to scar tissue. When a cap ruptures and the plaques' fatty cores are released into the bloodstream, a stroke or a transient ischemic attack (TIA) often results.

Advance: Researchers found a strong association between the integrity of the fibrous cap and recent occurrence of stroke or TIA. Seventy percent of individuals with ruptured fibrous caps and 50 percent with thin caps had a history of recent TIA or stroke, compared with only 9 percent of those with thick fibrous caps.

Implications: These findings raise the possibility that MRI can be used to detect plaques that are at risk of rupturing. If impending stroke could be predicted accurately, emergency interventions could be implemented to prevent it or to minimize its complications.

Yuan C, Zhang SX, Polissar NL, et al.: Identification of fibrous cap rupture with magnetic resonance imaging is highly associated with recent transient ischemic attack or stroke. Circulation 105: 181-185, 2002.

Risk Factors for Sleep-Disordered Breathing Identified

Background: Sleep-disordered breathing (SDB) is a common condition characterized by repeated airway obstruction that deprives the body of oxygen and disturbs sleep. Because SDB is associated with excessive daytime sleepiness and an increased risk of hypertension, heart failure, stroke, and diabetes, prompt and accurate diagnosis is important. Complaints of daytime sleepiness and sleeping difficulty are quite common among individuals seeking medical treatment; however little information exists to guide physicians in initiating treatment, especially in those patients with mild SDB.

Advance: Investigators found that obesity, habitual snoring, loud snoring, and frequent breathing pauses were associated with greater risk of moderate to severe SDB, although obesity and snoring were poor indicators for SDB in the elderly.

Implications: Sleep deprivation, daytime sleepiness, and sleep disorders are common but not widely recognized as personal or public health concerns. The study findings, however, indicate that sleep difficulties are associated with a substantial cost burden to the healthcare system in addition to their already established role as a factor in public health risks such as motor vehicle crashes, workplace accidents, reduced quality of life, depression, substance abuse, and development of cardiovascular diseases. Further study is necessary to develop strategies to identify and treat those with SDB.

Young T, Shahar E, Nieto FJ, et al.: Predictors of sleep-disordered breathing in community-dwelling adults. Arch Intern Med 162(8): 893-900, 2002.

Kapur VK, Redline S, Nieto FJ, et al.: The relationship between chronically disrupted sleep and healthcare use. Sleep 25(3): 289-296, 2002.

Use of Neuroimaging to Distinguish Between Normal and Pathological Changes in the Hippocampus

Background: Subtle memory and learning declines occur as we age, but it remains unknown whether the decline may herald a disease process or is simply part of normal aging. One particularly important brain structure for learning and memory function is the hippocampus. Subregions of the hippocampus are interconnected as a circuit so that disturbances in any one subregion can interrupt global function of this structure. Researchers often evaluate memory in humans with cognitive tests that assess global hippocampal function and are not helpful in distinguishing different causes of age-related memory decline. Furthermore, imaging the hippocampus globally without finer analysis does not allow one to distinguish normal age-related changes from ones that are targeted by disease processes. For example, with functional magnetic resonance imaging (fMRI), we can view brain structures that are a few millimeters in size, but even this resolution is insufficient for evaluating the minute subregions of the hippocampus. Visualization of the activity of different hippocampal subregions would be useful in determining whether a distinction can be made between normal and abnormal memory declines.

Advance: NIH-supported researchers developed a new method of fMRI that relies on oxygen use by the brain during rest and allows for visualization of signals from different subregions of the hippocampus. Using this new technique, they imaged the brains of 40 individuals ranging from 20-62 years of age and 30 individuals ranging from 70-88 years of age, all of whom were healthy individuals whose performance on neuropsychological tests was within normal limits. They found that some individuals showed a decline in signal intensity (function) in two hippocampal subregions, the subiculum and the dentate gyrus. The declines in function were continuous over the age range studied, indicative of normal decrement. However, other individuals showed a decline in function in another subregion, the entorhinal cortex, that was characterized by discontinuous decline independent of age that the investigators suggested was representative of abnormal decrement. Sixty percent of the oldest age group had significantly decreased signal in at least one hippocampal region; 40 percent showed no signal declines in the hippocampus compared to young adults. Among the elders with hippocampal decline, 23 percent had predominant decline in the subiculum or dentate ("normal") and 23 percent had predominant decline in the entorhinal cortex ("abnormal").

Implications: The findings from the study indicate that the memory decline seen with increasing age may stem from different mechanisms that impact the hippocampus. The authors suggest that those mechanisms that contribute to decreased function in the subiculum and dentate gyrus of the hippocampus produce normal age-related declines; those mechanisms that contribute to decreased function in the entorhinal cortex produce abnormal changes that may herald a neurodegenerative disease such as Alzheimer's disease. Further longitudinal study of these cases will be necessary to determine whether the loss of activity in different hippocampal subregions correlates with normal aging or Alzheimer's disease.

Small SA, Tsai WY, DeLaPaz R, Mayeux R, Stern Y: Imaging hippocampal function across the human life span: Is memory decline normal or not? Ann Neurol 51(3): 290-295, 2002.

Imaging Techniques Improve Alzheimer's Disease Diagnosis and Treatment

Background: Early and precise diagnosis of Alzheimer's disease (AD) benefits affected individuals and their families in a number of ways. However, a definitive diagnosis of AD can only be made at autopsy. New and improved imaging techniques, including refinement of positron emission tomography (PET) and magnetic resonance imaging (MRI), are improving our ability to characterize and diagnose the disease early, as well as giving us new options for tracking the effectiveness of treatments in the brain.

Advance: Researchers have made important progress in several areas:

· Tracking changes in brain metabolism. Investigators in several recent studies have identified specific metabolic changes in the brain that are characteristic of AD, and in one study have demonstrated that measuring patterns of brain metabolic changes can be used to diagnose AD with a high degree of accuracy.

· Tracking changes in brain structures. Changes in several brain structures are associated with AD. For example, researchers have found that the atrophy of an area of the brain known as the corpus callosum correlates with cortical metabolic decline and can be measured with MRI. In addition, investigators have recently found that atrophy of the hippocampus, a part of the brain affected by AD, is a fairly sensitive marker of AD-related pathologic damage and changes in cognitive function. MRI measurement of hippocampal volume may be useful for identifying early AD or for clinical assessment of cognitive decline.

· Imaging and evaluating AD's unique pathologic features. Researchers have developed ways to view and track AD's characteristic amyloid plaques in the brain. In one study in mice, investigators developed a radioactive tracer that is attached to an antibody that binds to the plaques, enhancing the ability to image them. In another mouse study, researchers developed a dye-based compound that the plaques soak up, again facilitating imaging.

Implications: These and other techniques may facilitate early diagnosis of AD, and may also provide effective methods of tracking treatment effectiveness, particularly through imaging amyloid burden in the brain.

Bokde AL, et al.: The effect of brain atrophy on cerebral hypometabolism in the visual variant of Alzheimer disease. Arch Neurol 58: 480-486, 2001.

Grady CL, et al.: Altered brain functional connectivity and impaired short term memory in Alzheimer's disease. Brain 124: 739-756, 2001.

Hampel H, et al.: Age transformation of combined hippocampus and amygdala volume improves diagnostic accuracy in Alzheimer's disease. J Neurol Sci 194: 15-19, 2002.

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Gosche KM, et al.: Hippocampal volume as an index of Alzheimer neuropathology: Findings from the Nun Study. Neurology 58: 1476-1482, 2002.

Jack CR, Jr. et al.: Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. Neurology 58: 750-757, 2002.

Lee HJ et al.: Imaging brain amyloid of Alzheimer disease in Vivo in transgenic mice with an Abeta peptide radiopharmaceutical. J Cereb Blood Flow Metab 22(2): 223-231, 2002.

Mathis CA, et al.: A lipophilic thioflavin-T derivative for positron emission tomography (PET) imaging of amyloid in brain. Bioorg Med Chem Lett 12: 295-298, 2002.

Scientists Identify a Genetic Cause for Recurrent Miscarriage

Background: Recurrent miscarriage affects approximately 1 of every 200 couples who attempt to have children. There are numerous possible causes of recurrent miscarriage, such as maternal infection, physiological and anatomical problems, hormonal factors, immune responses, or serious systemic diseases (such as diabetes or thyroid conditions). Approximately half of all recurrent miscarriages, however, cannot be attributed to any of these causes. Scientists believe that a large portion of recurrent miscarriages results from genetic problems. However, no causative gene has been found to date. One possible genetic cause in a subset of women involves the X chromosome. The X chromosome is unique in that it undergoes transcriptional inactivation in women. Females inherit two copies of every gene on the X chromosome, whereas males inherit only one. During early embryonic development, "transcriptional inactivation" occurs with one of the female's two X chromosomes being inactivated, leaving only one active X chromosome. Scientists believe this process normally occurs randomly and independently in each cell. However, some women do not show a random pattern but rather show preferential expression of one parent's chromosome in a majority of cells. This is referred to as "skewed X inactivation." Research studies suggest that women with highly skewed X inactivation miscarry more frequently than do women who have the normal random X chromosome inactivation. Furthermore, miscarriages are more likely to affect male fetuses. Since male fetuses receive only a copy of the mother's X chromosome, the chance of receiving the flawed chromosome is 50 percent. Thus, scientists anticipate the number of male babies born to mothers with skewed X inactivation will be half that of women without the condition. On the other hand, female fetuses receive a second, unflawed X chromosome from the father, which mitigates the effect of the flawed chromosome. These female fetuses live, but they will be at high risk for recurrent miscarriage during their reproductive years.

Advance: Researchers examined DNA samples from 120 women who had unexplained recurrent miscarriages and compared them with the DNA of a control group of 114 women with no similar history. The researchers found that, compared to the control group, the women who had a pattern of recurrent miscarriages showed: 1) a significantly higher frequency of skewed X inactivation, 2) a significant decrease in male children, and 3) the skewed X trait to be inherited (seen in four of six study families).

Implications: This study identifies a novel genetic cause that accounts for 25 percent of the previously unexplained cases of recurrent miscarriages. This defect can now be identified with DNA analysis for the skewed X inactivation. The next step will be to develop a blood test to assess the risk of miscarriage in future pregnancies. Identifying the affected women can help clinicians and genetic counselors provide appropriate fertility and reproductive counseling.

Lanasa MC, Hogge WA, Kubik CJ, Ness RB, Harger J, Nagel T, Prosen T, Markovic N, Hoffman EP: A novel X chromosome-linked genetic cause of recurrent spontaneous abortion. Am J Obstet Gynecol 185(3): 563-568, 2001.

Using Insulin Resistance to Identify Preeclampsia in Early Pregnancy

Background: Preeclampsia, which is characterized by pregnancy-induced high blood pressure and the presence of excess protein in the urine, complicates 3 to 4 percent of pregnancies and is a leading cause of illness and death for both the mother and the fetus. Currently, no early-pregnancy screening tests are available to predict the occurrence of preeclampsia, although elevated blood pressure, high body mass index (BMI), and fertility treatment are risk factors. Previous prevention strategies, such as calcium supplementation and aspirin therapy, have been mostly unsuccessful and currently the only effective treatment is induced delivery. It is still unclear whether insulin resistance is a cause of preeclampsia or a consequence of the condition. Scientists have used sex hormone binding globulin (SHBG), a protein produced by the liver, to measure insulin resistance among nonpregnant individuals; however, SHBG had not been studied during pregnancy or as an indicator of preeclampsia. As a unique marker of insulin resistance, SHBG is especially useful in clinical situations in which fasting blood samples are not collected routinely, such as during prenatal care. Low levels of SHBG indicate insulin resistance.

Advance: Researchers measured first-trimester SHBG levels in 45 women pregnant for the first time who subsequently developed preeclampsia. They were compared to a control group of 90 randomly selected first-pregnancy women with normal blood pressure throughout their pregnancies. In contrast to the control group, women who developed preeclampsia had significantly reduced first-trimester SHBG levels, indicating the presence of insulin resistance. These findings existed whether or not the women had a high BMI. In addition, women with preeclampsia delivered smaller birth weight babies at younger gestational ages and were more likely to deliver by Caesarean section.

Implications: This study demonstrates that measuring insulin resistance early in pregnancy could be a useful predictor of preeclampsia risk. Improving insulin sensitivity in high-risk women during early pregnancy may reduce the risk of preeclampsia. Furthermore, testing for SHBG levels early in pregnancy may be helpful in identifying lean, insulin-resistant women who otherwise would be considered at low risk for preeclampsia. Reducing the occurrence of preeclampsia could also reduce the number of low birth weight babies and reduce the frequency of Caesarean section deliveries. By routinely screening for and treating insulin resistance in all pregnant women, fewer women may incur the long-term risk of heart disease observed in those with a history of preeclampsia.

Wolf M, Sandler L, Munoz K, Hsu K, Ecker JL, Thadhani R: First trimester insulin resistance and subsequent preeclampsia: a prospective study. J Clin Endocrinol Metab 87(4): 1563-1568, 2002.

Home Uterine Activity Monitors Not Useful for Predicting Premature Birth

Background: Premature birth is the most important cause of infant illness and death and complicates 11 percent of all pregnancies in the United States. Premature infants can face life-threatening conditions. These conditions include: serious infections, respiratory distress, and damage to the intestines. To date, there is no reliable way to predict or to prevent premature birth.

Home uterine activity monitors (HUAMs) are portable devices that detect uterine contractions. They have been prescribed widely for patients in the hope that monitoring uterine contractions would identify women who are at risk of premature delivery. However, there was some question whether using HUAMs and measuring uterine contractions actually reduces the incidence of premature delivery.

Advance: A team of researchers supported by the NIH Network of Maternal Fetal Medicine Units collected data in a study of 306 pregnant women who used home uterine contraction monitor devices. Women who delivered before 35 weeks recorded more contractions when compared with women who delivered at 35 weeks or later. However, the researchers could not identify a pattern of frequency that effectively identified women who delivered premature infants. They concluded that, although increased frequency of uterine contractions is associated with an increased likelihood of premature delivery, measuring this frequency is not useful for predicting premature birth. Therefore, this study confirms that HUAMs are not able to predict or reduce the rate of premature delivery.

Implications: HUAMs do not identify women destined to have premature infants; this study explains the failure of this method to reduce the risk of premature delivery. HUAMs need not be prescribed for women at risk of giving birth prematurely because their use is of little value.

Iams JD, Newman RB, Thom EA, Goldenberg RL, Mueller-Heubach E, Moawad A, Sibai BM, Caritis SN, Miodovnik M, Paul RH, Dombrowski MP, McNellis D: Frequency of uterine contractions and the risk of spontaneous preterm delivery. N Engl J Med 346(4): 250-255, 2002.

New High Resolution Imaging Technique for Eye Tissue

Background: Diseases and disorders of the eye affect an enormous number of Americans every year. Today, over 100,000 people per year suffer from some form of trauma to the eye, over 6 million people per year suffer from degenerative retinal diseases, or diseases that affect the sensory membrane that lines the eye, and more than 3 million people in the U.S. suffer from glaucoma. Glaucoma is a series of conditions characterized by a particular form of damage to the optic nerve, the nerve responsible for carrying the images we see to the brain. Glaucoma is often associated with elevated intra-ocular pressure, or inner eye pressure. Currently, the mechanisms responsible for damage and successful therapy are not fully understood. While drug therapies are assumed to control the disease by reducing intra-ocular pressure, methods to evaluate or quantify changes in ocular (eye) blood flow have not previously existed. Measuring blood flow changes within the eye is particularly challenging, as the ocular tissue is opaque, making it hard for light rays or electromagnetic vibrations to penetrate deep into the eye. Therefore, the imaging of blood flow in the small arteries (arterioles) and veins (venules) located within the eye is extremely difficult. In addition, due to the small size of the vessels in the eye, imaging technique must be highly sensitive to provide necessary resolution, a measurement of the output quality of an image.

Advance: New high-frequency ultrasound scanning systems developed by NIH investigators now provide an unprecedented opportunity to image blood flow in the anterior segment of the eye. The resolution power of this novel technique represents an order of magnitude in improvement over existing techniques and provides the first non-invasive opportunity to evaluate blood flow in opaque tissues. A key aspect of this new technique is the development of new contrast agents that are acoustically activated. This technique allows researchers to develop a two-dimensional map of blood flow in the anterior segment of the eye, providing crucial information in the staging and diagnosis of various eye diseases and disorders.

Implications: High-resolution and non-invasive imaging capabilities are crucial to diagnosing eye diseases, assessing disease progression and severity, and evaluating treatment methods. The ability to diagnosis and monitor the physiology of the eye will also help to combat major causes of blindness. In addition, information about normal eye physiology, as well as age-dependent variations, will be paramount to fully understanding the mechanisms of all eye diseases and disorders.

Allen JS, Donovan JM, Ferrara KW: Dynamics of Therapeutic Ultrasound Contrast Agents. Ultrasound in Med Biol 28(6), 805-816, 2002.

New Digital Tools to Evaluate Child Development Across Ethnic Boundaries

Background: Bone age assessment is a common diagnostic procedure performed on children to evaluate normal growth and to identify possible growth disorders, malformations and bone abnormalities. The traditional method used for bone age assessment is to compare a left-hand radiograph (x-ray) taken from the patient against a reference atlas. Currently, this atlas contains a small number of normal left-hand pattern standards and was developed in the1950s by Greulich and Pyle. Unfortunately, these reference standards do not accurately reflect skeletal development in children and adolescents of European, African, Hispanic or Asian descent. Therefore, the use of this atlas as a standard across such ethnically diverse populations has led to significant inconsistencies in the determination of skeletal development. Today, population diversity in the United States continues to increase, suggesting that certain practices in bone age assessment be reassessed.

Advance: NIH researchers have recently developed a digital atlas containing a large set of normal hand and wrist images of children from four ethnic groups. This atlas is comprised of over 1,100 reference images compiled from computed radiography (CD) and digitized film and contains computer-extracted bone objects and quantitative features that can be used to more thoroughly evaluate skeletal development. Images in the database are evenly distributed across a wide range of healthy children, including infants and adolescents; males and females; and children of European, African, Hispanic and Asian descent. Furthermore, the digital atlas format supports both Web-based access and automated diagnosis. For example, measurements taken from a patient's hand image are compared with patterns from the atlas database to assess bone age.

Implications: This new resource will allow physicians to more accurately assess skeletal development in children and adolescents across various ethnicities, enhancing the diagnosis and management of a variety of metabolic and growth disorders. The atlas can also be used in planning orthopedic procedures. Furthermore, the development of a digitized and automated diagnostic tool represents a significant contribution to practices in imaging sciences, enabling many medical advances in the upcoming years.

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Real-time, Ultra-high Resolution Imaging

Background: The increasing number of laser-based eye surgeries in the United States creates a critical need for ultra-high resolution imaging capable of displaying information in real-time. While there are many techniques available, including biopsy, video, and thermal imaging, these methods cannot resolve the time and depth information necessary to verify current procedures. Laser irradiation, a method that exposes the eye to radiation, is also becoming widely used to treat a variety of vascular disorders, but the treatments are often incomplete due to an inability to accurately assess the effectiveness of a given therapy. A new technique called Optical Coherence Tomography (OCT) holds promise as a method to non-invasively obtain structural and functional information at the micron scale, enabling the evaluation of a wide range of clinical disorders.

Advance: OCT is an ultra-high resolution imaging method which may be able to overcome many of the limitations of the current techniques used to monitor the anterior portion of the eye. Until recently, OCT systems required approximately 20 seconds to display an image with only moderate resolution. Recent technological advancements by NIH researchers have led to the development of a real-time, high-resolution imaging system that reduces imaging flaws attributed to patient motion and device misalignment. In addition, hand-held OCT systems have been developed to allow more convenient imaging of the anterior segment of the eye during routine clinical examinations. Recent studies have also expanded the use of OCT systems to the lung, stomach, and intestines.

Implications: The existence of portable, non-invasive, ultra-high resolution imaging devices will be invaluable in the rapid diagnosis and treatment of patients with a variety of disorders. OCT systems will be important for the early detection of cancers of the lung, stomach, and intestines, outcome assessment of laser eye surgeries, evaluation of common eye disorders, and monitoring of patients with vascular complications associated with diabetes, glaucoma, and age-related diseases and disorders.

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New Gene Discovered as a Cause of Hereditary Deafness

Background: Within the last seven years, over 60 different genes for nonsyndromic hereditary hearing impairment have been mapped and over twenty identified by positional cloning. In addition, several genes essential for normal auditory development and/or function have been identified using mouse models. Recently, scientists have discovered a new gene of unknown function, TMC1, in which mutations cause deafness. TMC1 was discovered through genetic mapping studies of large families with hereditary hearing loss. These mutations can cause two different types of hereditary hearing loss: profound congenital deafness which is inherited in a recessive fashion, and delayed onset, progressive hearing loss which is inherited in a dominant pattern.

Advance: NIH intramural scientists have identified a mutation in the mouse Tmc1 gene which causes similar types of dominant and recessive hearing loss found in large human family studies. Mouse models permit studies of inner ear structure that are not possible in humans. In mice, mutations in the Tmc1 gene causes defects in the function of the specialized sensory cells of the inner ear, known as hair cells. Hair cells detect and convert the physical stimulus of sound into electrical impulses sent to the brain via the hearing nerve. Mutations in mouse Tmc1 either directly or indirectly blocks this nerve signaling process.

Implications: This research contributes to new models for studying specific forms of human deafness. Since studies of the inner ear structures are not easy to conduct in humans, using mouse models allow scientists to rapidly isolate the genetic mutations involved with hearing impairment. This finding will lead to new diagnostic strategies for hearing impairment and will help scientist develop new therapies for genetic defects of the inner ear.

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Vreugde S, Erven A, Kros CJ, et. al.: Beethoven, a mouse model for dominant, progressive hearing loss DFNA36. Nat Genet 30: 257-258, 2002.

Hearing Loss Due to Thyroid Hormone Resistance

Background: Resistance to thyroid hormone (RTH) is a hereditary disorder that causes tissues and organs to respond to the hormone ineffectively. The thyroid is a gland in the neck that regulates heart rate, metabolism, growth, mental function, energy and mood. This disorder is caused by a mutation in the THRB gene which encodes one subunit of a receptor for thyroid hormone, Trß. Individuals with RTH may also have a hearing impairment. Although thyroid hormone is known to be required for normal development of the inner ear, the mechanism by which THRB mutations cause hearing loss has been unknown.

Advance: NIH intramural scientists are studying a mouse model for RTH that was developed by scientists at the National Cancer Institute. The results of the study indicate that RTH causes hearing loss by making the sensory tissue of the inner ear (cochlea) and the sensory hair cells develop abnormally. It was previously known that mice lacking all Trß receptors have hearing loss, although their hearing loss is not due to abnormal structural development of the cochlea. In contrast, the mutant Trß protein in RTH is not only defective but disrupts the functions of other genes that are required for cochlea development. One of these genes, Tra, is likely to be another receptor subunit for thyroid hormone.

Implications: This research uncovers the previously unknown relationship between thyroid hormone and its affect on the genetic mutations causing structural damage to the inner ear. Further research could lead to new diagnostic strategies for individuals with hearing impairment and may also provide scientists with further information about the structure of the ear that could lead to future treatment.

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Children with Speech-Sound Disorders are at Risk for Later Academic Impairments

Background: Children with speech-sound disorders often have difficulties in other areas of language as well. Previous studies have demonstrated that speech, language and reading difficulties are common in families of children with vocal-sound disorders. Poor awareness of vocal sound skills and a weakness in vocal sound classification in verbal memory may put children of preschool age with speech-sound disorders at risk for later spelling difficulties. Previous studies of children with early speech sound disorders have not examined spelling outcomes in relation to the type of early speech and/or language disorder.

Advance: In a recent NIH-supported study, the spelling errors of 52 children with history of speech-sound disorders were analyzed to predict the association between weaknesses in spoken language skill in early childhood and school-age spelling abilities. Children four- to six-years old in 87 families were recruited to study the correlation of early speech-sound disorders with spelling impairments. Based on their preschool language skills, the children were assigned to one of two study groups if they were diagnosed with a speech-sound disorder or speech-sound disorder with additional language impairment. Follow-up measures were administered in the areas of speech-sound, spelling, reading, language and the collective influence of the family. The findings of this study support previous research that suggests that children with early speech-sound disorders are at risk for later spelling difficulties. Spelling difficulties may come from speech-sound processing deficits that persist even after the speech-sound disorder is resolved later in life. Evidence from studying these families raises the possibility of a common genetic cause for speech/language and written language disorders. In this study, the number of family members with speech, language, reading and spelling disorders exceeded expected frequency for these disorders in the general population. Although the genetic cause for these disorders is not known, specific signs of the disorder suggest that gender may be a factor because brothers were also more likely to have the disorder than sisters.

Implications: The findings of this study reveal that preschool children with speech-sound disorders are at risk for later spelling impairments even after productive speech disorders have resolved. Preschool children with both speech-sound and language disorders are likely to have more severe spelling problems than preschoolers with only speech-sound disorders. Careful follow-up of children with both disorders are needed even after the speech-sound disorder has resolved. In addition, a family history of spelling difficulties may identify children who may be at risk for developing written language disorders.

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Genetic Insights into Pancreatitis and Pancreatic Cancer

When the pancreas produces enzymes to digest food, why don't those enzymes also digest the pancreas? Sometimes, they do – and with painful and potentially fatal consequences – as in the case of the disease hereditary pancreatitis. Several years ago, researchers discovered a mutation that abolishes one of the body's key safeguards against destruction of the pancreas by the very digestive enzymes it manufactures. This scientific breakthrough marked the beginning of a series of genetic discoveries that are providing new insights into hereditary pancreatitis, pancreatitis that arises for no known reason (idiopathic) and pancreatic cancer.

Patients with pancreatitis usually experience severe pain. As the pancreas becomes progressively injured and inflamed, in part as a result of infiltrating inflammatory cells, it can no longer secrete enough enzymes into the duodenum (a part of the small intestine) for digesting food. As pancreatitis advances, the cells of the pancreas that produce the vital hormone insulin become damaged as well. Without insulin, the patients develop diabetes. Currently, treatments exist to help manage the pain and digestive enzyme deficiency associated with pancreatitis, but there are no cures or preventative therapies. Patients suffering long-term from pancreatitis are also at dramatically increased risk for pancreatic cancer. One of the most devastating of all malignancies, pancreatic cancer nearly always kills within a year of diagnosis, and often within six months.

Clinicians had long associated pancreatitis with alcoholism. While excessive alcohol consumption clearly plays a role in many pancreatitis cases, researchers recognized a hereditary form of pancreatitis as early as 1952. An attempt to find a hereditary pancreatitis gene in the 1970s, however, was unsuccessful. The identification of genes associated with pancreatitis awaited the advent of modern molecular and genetic technology.

In 1996, scientists found the first gene linked to a form of pancreatitis called hereditary pancreatitis. Hereditary pancreatitis generally strikes in childhood and is readily transmitted from one generation to another in a family, because a person who receives a mutated copy of the gene from just one parent can develop the disease, even if the copy from the other parent is normal. This gene encodes the protein cationic trypsinogen, which is an inactive precursor form of the digestive enzyme trypsin. Trypsin helps digest proteins from food so that their amino acid building blocks can be absorbed and reassembled into new proteins for the body. Trypsin strikes only at particular amino acids, one of which is the amino acid arginine. To avoid digestion of the pancreas, trypsinogen normally does not become activated within the pancreas itself to form trypsin. If it does, the body has what scientists call a “fail-safe” line of defense: for the greater good, the prematurely-active trypsin commits molecular hara-kiri, slashing itself at one of its own arginine amino acids. Many people with hereditary pancreatitis have a mutation in the trypsinogen gene that alters this arginine, consequently disabling the defense mechanism. By studying different patients with hereditary pancreatitis, researchers have also identified other mutations in this gene; two novel mutations were identified in 2002. The continued

identification of mutations that confer susceptibility to hereditary pancreatitis is useful for the design of diagnostic tests.

Among people whose genetic make-up would predispose them to hereditary pancreatitis, approximately one in five will not actually develop the disease. To investigate why, researchers studied pairs of identical twins at genetic risk. Surprisingly, in three out of seven pairs of identical twins studied, one twin had developed the disease, but the other did not. Because identical twins share chromosomal gene sequences and most types of environmental factors, the results of this study, showing differences between identical twin siblings, clearly suggest that other types of genetic factors ("epigenetic factors"), environmental factors, or chance events may also play a part in the development of hereditary pancreatitis. The initiation and progression of pancreatitis is believed to involve a long chain of activation of different enzymes, and the disease is also precipitated by external factors such as food and drinking. A better understanding of the complex interactions between different types of genetic and environmental factors will be a major challenge for future investigations.

Knowledge of genetic influences on hereditary pancreatitis has also helped in the assessment of environmental risk factors for pancreatic cancer, because people with hereditary pancreatitis are at increased risk of pancreatic cancer. Scientists recently evaluated hereditary pancreatitis patients to determine the effect of smoking on the development of pancreatic cancer. Alarmingly, the researchers found that the cancer developed 20 years earlier in smokers. It is not yet clear whether smoking also has this effect on the age of onset of pancreatic cancer among people who don't have hereditary pancreatitis.

Several years after the discovery that mutations in the trypsinogen gene cause hereditary pancreatitis, scientists identified mutations in a different gene that are associated with idiopathic pancreatitis. This gene encodes a protein called SPINK1, which normally helps to protect the pancreas by inhibiting the digestive functions of prematurely-activated trypsin. *SPINK1* gene mutations occur in families afflicted with idiopathic pancreatitis and seem associated with early disease onset. However, the effects are far more subtle than those of mutations in the trypsinogen gene that cause hereditary pancreatitis. Further, *SPINK1* mutations are relatively common in people who do not have pancreatitis. As a result, dissecting the nature of the association between *SPINK1* mutations and pancreatitis remains challenging.

The identification of another gene associated with idiopathic pancreatitis had its origins in research on a seemingly unrelated disease, cystic fibrosis, which is caused by mutations in the *CFTR* gene. One of the characteristic symptoms of cystic fibrosis is the presence of thick mucus in the lungs. However, CFTR protein function is also important in the pancreas, and some cystic fibrosis patients get pancreatitis. Scientists recently found that many idiopathic pancreatitis patients harbor a particular pattern of *CFTR* mutations. Different types of mutations affect a gene's function to a greater or lesser extent. While people who inherit severe mutations in both copies of the *CFTR* gene (one from each parent) develop cystic fibrosis, idiopathic pancreatitis patients with *CFTR* mutations often have a combination of one severe and one milder mutation.

With the discovery in 1996 of the link between trypsinogen and hereditary pancreatitis, the finding two years later, in 1998, that many idiopathic pancreatitis patients harbor *CFTR* mutations, and the association in 2000 of *SPINK1* with idiopathic pancreatitis, it would seem that another major genetic discovery in pancreatic disease would arrive in 2002. One did. The investigator who led the research on the first hereditary pancreatitis gene teamed up with a group of scientists to bring to light the first genetic defect specific to pancreatic cancer. By applying state-of-the-art genomic techniques and intensive surveillance for signs of cancer and precancer to the study of a large family afflicted with this disease, the scientists were able to pin down the location of a pancreatic cancer susceptibility gene to a specific region of chromosome 4. This was a major accomplishment, as the rapid death of pancreatic cancer patients, as well as other aspects of this disease, make genetic analysis extremely difficult. Currently, the scientists are working to identify the mutant gene in this chromosomal region, as its identification could shed new light on pancreatic cancer and provide a means for early diagnosis of patients at risk.

Screening patients for genetic mutations can have many potential health benefits, including ruling out other possible causes of symptoms and alerting patients at risk to seek early medical intervention. However, the results of a genetic test may also have serious implications for patients and their family members, including affecting their ability to obtain health or life insurance and influencing reproductive choices. Deeply concerned about the ethical and social implications of genetic testing for pancreatitis, a group of investigators who study pancreatitis recently surveyed individuals participating in a hereditary pancreatitis genetic research study. The most common reasons the participants gave for joining the study were to help current family members and future generations and to obtain genetic testing. The major concern expressed by the participants was the fear of insurance discrimination. The most common reasons for sharing their results were to provide medical information to their families and to improve their own medical care.

As scientists and clinicians continue to build upon these achievements in research on the genetics of pancreatitis and pancreatic cancer, they will better understand the molecular mechanisms underlying these diseases. These advances will also facilitate research on environmental factors that may affect disease onset and progression in genetically-susceptible individuals. The identification of mutations that cause hereditary pancreatitis has already led to

the development of gene-based methods to evaluate a person's risk for this disease. Increased understanding of genetic factors associated with different forms of pancreatitis and pancreatic cancer will undoubtedly also suggest new strategies for diagnosis, treatment, and prevention.